DTPA and MAG3 scintigraphy in Acute Renal Allograft Dysfunction: Comparison of Diagnostic Values

Akut Renal Allograft Disfonksiyonunda DTPA ve MAG3 Sintigrafileri: Tanısal Değerlerin Karşılaştırması

DTPA/MAG3 Scintigraphy in Renal Transplants

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Özet

Amaç: Akut renal allograft disfonksiyonunda sintigrafik renal fonksiyon parametrelerinin kullanılan radyofarmasötik tipine göre karşılaştırılması ve erken tanıdaki değerlerinin incelenmesi. Gereç ve Yöntem: Akut renal disfonksiyon (ARD) tanılı 28 hastaya (20 erkek, 8 kadın; yaş ortalaması 33±2) böbrek sintigrafisi, doppler ultrasonografi ve renal biyopsi işlemleri yapıldı. Böbrek sintigrafileri her hastada iki ayrı radyofarmasötik form (Tc-99m DTPA ve Tc-99m MAG3) kullanılarak ardışık iki günde gerçekleştirildi. Her iki çalışma gününde, serum kreatinin, kan-üre azotu, total protein, albumin, siklosporin A/takrolimus düzeyleri ölçüldü, kan ve 24 saatlik idrardan kreatinin klirensi hesaplandı. Sintigrafik incelemede peak/plato oranı (PPR), Hilson Perfüzyon indeksi (HPI), delta-P, vasküler washout, transplant perfüzyon ve fonksiyon indeksi, uptake (R/B), pik zamanı (Tmax), pik yarı zamanı, glomerüler filtrasyon hızı, parankimal retansiyon (R20/3) parametreleri kullanıldı. Parametreler için her iki sintigrafik inceleme grubu arasında farklılık istatistiksel olarak analiz edildi. Bulgular: HPI ve R20/3 değerleri arasındaki farklılık istatistiksel olarak anlamlı değilken (p>0.05), Tmax ve R/B değerleri için farklılık anlamlı bulundu (p<0.05). En sensitif parametre Tc-99m DTPA grubu için PPR ve Tc-99m MAG3 grubu için R/B olarak saptandı. Renal fonksiyonlarda bozulmayı belirlemede Tc-99m DTPA ve Tc-99m MAG3 renal sintigrafi çalışmalarının sensitiviteleri sırasıyla %75 ve %57.1 olarak bulundu. Tartışma: Perfüzyon ve parankimal fonksiyon parametreleri birlikte değerlendirildiğinde akut renal allograft disfonksiyonunun erken dönemde tanınmasında Tc-99m DTPA sintigrafisinin performansının daha iyi olduğu sonucuna varıldı.

Anahtar Kelimeler

Böbrek Transplantasyonu; Tc-99m MAG3; Tc99m-DTPA; Doku Reddi

Abstract

Aim: To compare scintigraphic renal function parameters according to the radiopharmaceuticals used in acute renal allograft dysfunction and to evaluate their value in early diagnosis. Material and Method: Renal scintigraphy, Doppler ultrasonography, and renal biopsy were conducted on 28 patients (20 males, 8 females; mean age 33 ± 2 years) with the diagnosis of acute renal dysfunction (ARD). Renal scintigraphy was done by using two different radiopharmaceuticals (Tc-99m DTPA and Tc-99m MAG3) on each patient, on consecutive days. On both days the serum creatinine, blood urea nitrogen, total protein, albumin, and cyclosporine A/tacrolimus levels were measured and creatinine clearance was calculated from blood and the 24-hour urine. On scintigraphic evaluation, the peak to plateau ratio (PPR), Hilson perfusion index (HPI), delta-p (ΔP), vascular washout, transplant perfusion and function index, uptake (R/B), peak time (Tmax), peak half time (T½), and parenchymal retention (R 20/3) parameters were used. The difference between the parameters of both scintigraphic evaluation groups were statistically analysed. Results: While the difference between HPI and R20/3 values was not statistically significant (p>0.05), the difference between Tmax and R/B values was found to be significant (p<0.05). The most sensitive parameter was found to be PPR for the Tc-99m DTPA group and R/B for the Tc-99m MAG3 group. The sensitivity of Tc-99m DTPA and Tc-99m MAG3 renal scintigraphy studies in determining deterioration of the renal functions was found to be 75% and 57.1%, respectively. Discussion: When perfusion and parenchymal function parameters were evaluated together, it was concluded that the performance of Tc-99m DTPA was better in early diagnosis of renal allograft dysfunction.

Keywords

Kidney Transplant; Tc-99m MAG3; Tc99m-DTPA; Graft Rejection

DOI: 10.4328/JCAM.4572 Received: 22.04.2016 Accepted: 06.05.2016 Printed: 01.01.2017 J Clin Anal Med 2017;8(1): 14-8
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Introduction

The early diagnosis and treatment of function disorders that shorten the life of grafts after kidney transplantation can prevent or delay the progression of acute dysfunctions to the chronic stage. The most common causes of renal transplant dysfunction are acute rejection (AR), chronic nephropathy (CrAN), acute tubular necrosis (ATN), and cyclosporin A (CyA) nephrotoxicity. While several diagnostic methods are used in the differential diagnosis of these causes, there is no single specific diagnostic method. The quantitative data obtained through serial renal scintigraphic imaging done after surgery contributes to the ruling out of clinically significant complications [1].

Tc-99m mercaptoacetyltriglycine (MAG3), excreted through tubular secretion, and Tc-99m diethylenetriamine pentaacetic acid (DTPA), secreted through glomerular filtration, are often used for renal allograft scintigraphy. DTPA is suitable for determining perfusion and glomerular filtration rate. There are papers reporting that MAG3 is a more suitable choice in those with weak renal function due to high renal extraction [2]. The treatment protocol can be determined by comparing the serial scintigraphic images of the renal allograft [2,3]. It is reported that MAG3 should be preferred to DTPA because of its better extraction in patients who have developed a dysfunction [4,5]. In fact, DTPA is more quickly affected by decreased renal function and a decrease in concentration is observed. Therefore, we expect DTPA to be more sensitive in acute allograft dysfunction. In our routine screenings done with this agent, we observed that the pattern of uptake, first showing a rise, then a decrease, and finally reaching a plateau on the perfusion time-activity curve, was the first parameter to be disrupted in cases of intrarenal pressure increase such as AR. This pattern was not present with MAG3 in our patients. In this study, the various perfusion and parenchymal function parameters of DTPA and MAG3 in renal transplant recipients developing acute renal allograft dysfunction (ARD) were compared and parameters that will be more helpful in early diagnosis were considered. We also investigated whether the difference observed in the extraction fraction between these two radiopharmaceuticals was superior for the differential diagnosis in allograft dysfunction.

Material and Method

Patients

Twenty-eight patients whose renal functions were stable after transplantation and who were later referred due to high levels of creatinine were prospectively included in the study (20 males, 8 females; age range 15 to 63 years; mean age 33 ± 2 years). Patients with normal renal functions following transplantation were not included. A total of 56 scintigraphic studies done with DTPA and MAG3, with one day in between, were included in the study. The study was conducted according to the World Medical Association Declaration of Helsinki (revised in 2000, Edinburgh). During the scintigraphic study, 18 patients were using CyA and 10 were using Tacrolimus. Also, a Doppler ultrasonography (US) and a renal biopsy were done on the patients either on the same day or the following day. On both scintigraphic study days, the serum creatinine, blood urea nitrogen (BUN), total protein and albumin, and CyA or Tacrolimus levels were checked. Creatinine clearance (CrCl) was calculated from blood and the 24-hour urine.

Scintigraphic technique

The imaging was done with a dual-head gamma camera (Siemens, eCAM, Germany) with a low energy all purpose (LEAP) collimator following the intravenous bolus injection of Tc-99m DTPA at a dose of 259MBq and of Tc-9m MAG3 at a dose of 185MBq with the patient in the supine position, over the iliac fossa. The images were recorded within the 140 keV± 20% energy range, using a 64x64 matrix and 1.23 zoom factor. 60 images (1 sec/frame) were taken for the perfusion phase, and 40 images (30 sec/frame) were taken for the parenchymal phase. The patients were evaluated with a Doppler US on the same day or within 24 hours. The scintigraphic findings were visually and quantitatively evaluated. We calculated Hilson perfusion index (HPI) [3], peak to plateau ratio (PPR) [6], delta-P (ΔP) [6], vascular washout (VW) [6,7], transplant perfusion index (TP) [3], time to maximum activity (Tmax) [5], time to half of maximum (T ½) [5], parenchymal retention (R20/3) [8], uptake (R/B), transplant function index (TF) [3], and glomerular filtration rate (GFR) [9,10]. Calculation methods and normal values of these parameters are described in Table 1.

Table 1. The method of calculation of renal graft perfusion indices and parameters related to the uptake and excretion, with normal reference values.

Parameter	Method of calculation	Normal range
HPI	Calculated from the ratio of the area under the arterial curve and the renal curve.	<96%
PPR	Ratio of counts at peak perfusion to that at plateau that was calculated from DTPA vascular curve.	1.48-1.62
ΔP	Time between peaks of iliac and graft curves	2.4-3.4 s
VW	The graft perfusion curve of the peak value of the time to be halved	13-17 s
TP	Calculated from the first 100 seconds of a MAG3 perfusion curve by Bubeck method and taking into account peak intensity and the increase of the maximum activity during the arterial phase.	
T max	Calculated from time-activity curves of the kidneys that is time to reach maximum activity in the renogram curve	240±60 s
T ½	The washout time to reach half activity of time-activity curves of the kidneys	660±120 s
R20/3	Percentage of the peak activity retained at 20 min in time-activity curves	>0.8
R/B	The ratio of background activity of the renal activity in 3 minutes in time-activity curves	
TF	Calculated from the first 100 seconds of aMAG3 perfusion curve by Bubeck method	
GFR	Calculated using camera-based methods (Gates methods) from Tc-99m DTPA study	>45 mL/min

ΔP: Delta-P, GFR: Glomerular filtration rate, HPI: Hilson perfusion index, PPR: Peak to plateau ratio, R20/3: Parenchymal retention, R/B: Uptake, T max: Time to maximum activity, T ½: Time to half of maximum, TF: Transplant function index, TP: Transplant perfusion index, VW: Vascular Washout

Statistical Analysis

The HPI, R/B, R20/3, Tmax, BUN, and creatinine levels obtained with both agents were compared as binary variables with an independent sample t-test. P values <0.05 were considered as statistically significant. The correlation between the parameters was assessed using Pearson's correlation test; a correlation

of p<0.05 was considered as significant. Data were expressed as mean±standard error of the mean. Sensitivity and specificity for both agents were calculated by determining at least two of the most sensitive parameters for DTPA and MAG3. Data analyses were done with SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA).

Results

No significant difference was observed between the creatinine values of the patients obtained on DTPA and MAG3 studies, which were one day apart (p>0.05). There was also no significant difference between the BUN values of the patients obtained on DTPA and MAG3 studies, which were one day apart (p>0.05). Creatinine levels were at the upper normal limit in two patients and higher than normal in 26 patients. BUN values were high in all patients. CrCl was found to be lower than normal in all patients in whom it was calculated. CyA and Tacrolimus levels were within normal limits in all patients.

Biopsy and Doppler US results

The biopsy results of the patients were as follows: Grade I AR (n=4), grade IIB AR (n=1), grade I (CrAN) (n=4), grade II CrAN (n=1), grade I CrAN with chronic CyA nephrotoxicity (n=1), acute tubulointerstitial nephritis (ATIN) (n=2), tubular epithelial injury (TEI) (n=3), nonspecific changes (NS) (n=3), and normal findings (n=8). No biopsy was performed on one patient who was being followed for a year with a CrAN diagnosis. A high resistance flow was detected on renal Doppler US of the two patients with AR and of one patient with CrAN. In the other patients, Doppler US findings were within normal limits.

Scintigraphic study findings

The average values of the parameters obtained with both agents and statistical relationships between these parameters are shown in Table 2. The DTPA perfusion curve with peak/plateau pattern was observed in nine patients and PPR values of these patients were normal. The DTPA perfusion curve with an early plateau was observed in 15 patients; their PPR values were found to be lower than 1.48. PPR and VW were not calculated in four patients in whom a gradually rising curve pattern was observed. In 24 cases with other patterns, the PPR mean value was calculated as 1.42±0.05. The stratification of the peak/plateau patterns according to pathological diagnosis of the patients is shown in Table 3. The PPR values showed negative correlation (r=-0.688; p<0.05) with VW and positive correlation (r=0.434; p<0.05) with TF. On the other hand, in the MAG3 perfusion curve, the second phase corresponding to early tubular extraction, which normally shows a gradually rising curve pattern, was flattened in three patients. With biopsy, AR was detected in one of them and CrAN was detected in two of them (Fig 1a,b; Fig 2a,b).

In 24 patients with a peak/plateau pattern in the DTPA perfusion curve, VW was found to be high. The delta-P value was within normal limits in five patients. There was no correlation between the delta-P value and other parameters (p>0.05). The HPI mean values derived from the DTPA and MAG3 perfusion

Table 2. Mean values of quantitative parameters used in the evaluation of renal transplant function (mean values±standard error mean)

Parameter	Mean Values (DTPA)	Mean Values (MAG3)	P value*
Perfusion phase			
HPI (%)	84±7.19	84.22±8.85	P>0.05
PPR	1.42±0.05	–	
ΔP (s)	4.8±0.3	–	
VW (s)	30.58±2.1	–	
TP	–	5.3±0.64	
Parenchymal phase			
T max (min)	3.73±0.33	5.69±0.45	P<0.05
T ½ (min)	19.25±0.24	17.89±0.92	P<0.05
R20/3 (%)	80.52±3.03	87.07±6.01	P>0.05
R/B	3.52±1.3	13.45±1.35	P<0.05
TF	-	1.92±0.22	
GFR (mL/min)	54.99±19.87	-	

ΔP: Delta-P, GFR: Glomerular filtration rate, HPI: Hilson perfusion index, PPR: Peak to plateau ratio, R20/3: Parenchymal retention, R/B: Uptake, T max: Time to maximum activity, T ½: Time to half of maximum, TF: Transplant function index, TP: Transplant perfusion index, VW: Vascular Washout

Table 3. The stratification of the peak/plateau pattern in the graft perfusion time activity curve obtained with Tc-99m DTPA according to pathological diagnosis

	Peak/plateau pattern	Peak-early plateau	Irregular peak-early plateau	Rising curve pattern
Number of patients	9	10	5	4
Histopathological Diagnosis				
AR	1	1	2	1
CrAN	1	1	2	3
Tubular epithelial İnjury	1	2		
Nonspecific changes	1	2		
Acute tubuluinterstitial Nephritis		2		
Normal	5	2	1	

AR: Acute rejection, CrAN: Chronic allograft nephropathy, PPR: Peak to plateau

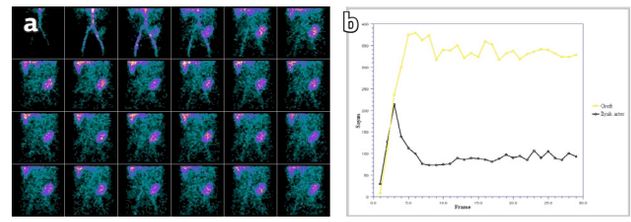

Fig 1. Perfusion images obtained with Tc-99m DTPA in a patient in whom acute rejection was detected and the perfusion time-activity curve. It is observed that the peak/plateau pattern in the graft perfusion curve is disrupted. Transplanted kidney perfusion is decreased (a,b).

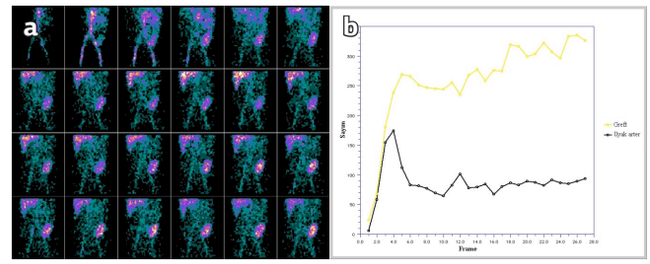

Fig 2. Perfusion images obtained with Tc-99m MAG3 belonging to the same patient in whom acute rejection was detected and the perfusion time-activity curve (a,b).

curves were within normal limits. There was no statistically significant difference between them (p>0.05). However, a positive correlation was detected between HPI values derived from DTPA and MAG3 (r=0.743; p<0.05).

There was a significant difference between the Tmax values obtained with both radiopharmaceutical agents (p<0.05) and a positive correlation was found (r=0.608; p<0.05). In eight patients whose Tmax values with DTPA were normal, the Tmax values with MAG3 were detected to be prolonged. T½ was found to be over 10 minutes with DTPA in all patients, below 10 minutes with MAG3 in four patients (CrAN in one patient, normal biopsy findings in three patients), and prolonged in the others. There was no significant difference between the R20/3 values obtained with both radiopharmaceutical agents (p>0.05) and a positive correlation was found (r=0.670; p<0.05). In the DTPA study, the R20/3 value was above 80% in 14 patients (AR in five patients and CrAN in three patients) (Fig 3a,b). In the MAG3 study, the R20/3 value was above 80% in 15 patients (AR in three patients and CrAN in five patients) (Fig 3c,d). A statistically significant difference (p<0.05) was found in the R/B values obtained with both agents and showed a positive correlation with both agents (r=0.650; p<0.05) (MAG3/DTPA mean R/B ratio was 3.8). The TP and TF indices had a positive correlation (r=0.853, p<0.05) with each other. The TP had a negative correlation with the HPI values obtained with DTPA and MAG3 (r= -0.393, r= -0.456, p<0.05, respectively). Also, TF had a negative correlation with the HPI values obtained with DTPA and MAG3 (r= -0.572, r= -0.535; p<0.05, respectively). The CrCl value had a positive correlation with GFR (r=0.508; p<0.05). GFR was found to be below normal in 10 patients (CrAN in four patients, AR in four patients). GFR had a negative correlation with creatinine values obtained with DTPA and MAG3 on the day of the study (r= -0.659 and r= -0.685, p<0.05, respectively).

The sensitivities of the parameters are given in Table 4. According to this, the most sensitive parameters in determining acute and chronic allograft dysfunction were PPR for DTPA and R/B for MAG3. The sensitivities of Tc-99m DTPA and Tc-99m MAG3 studies were found as 75% and 57.1%, respectively.

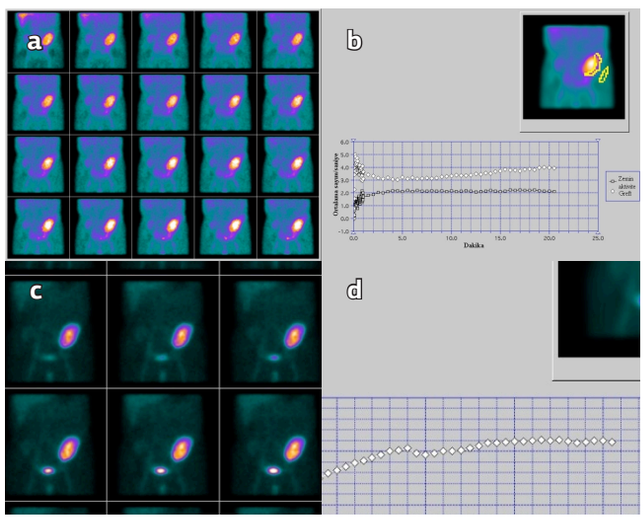

Fig 3. Concentration images obtained with Tc-99m DTPA in a patient in whom acute rejection was detected and the renogram curve. The transplanted kidney concentration is delayed and decreased and a significant parenchymal retention is detected (a,b). Concentration images obtained with Tc-99m MAG3 belonging to the same patient in whom acute rejection was detected and the renogram curve. The transplanted kidney concentration is delayed and decreased and parenchymal retention is detected (c,d).

Discussion

After a successful kidney transplant operation in end-stage renal failure, the patients no longer need dialysis and their quality of life is improved [11]. Despite effective use of immunosuppressants, acute allograft dysfunction and particularly acute rejection can prevent the success of a renal transplantation [12]. Renal transplant scintigraphy plays an important role in the assessment and monitoring of graft functions. In grafts functioning normally, the DTPA perfusion time-activity curve of the allograft shows a peak followed by a plateau. Because this peak and plateau pattern is not observed in perfusion curves obtained with tubular agents, it may be advantageous to use DTPA scintigraphy [13, 14]. If a graft activity peak is observed within six seconds after activity is seen in the neighbouring artery in the DTPA perfusion curve and if there is a decisive decrease after the peak, then the perfusion is assessed as normal [15]. In our study, the PPR values obtained with DTPA were consistent with the perfusion curve pattern. Early plateau resulted in our obtaining low PPR and prolonged VW values. In our patients who were diagnosed to have AR and CrAN (with the exception of one AR and one CrAN patient), the curve pattern was disrupted. Therefore, we concluded that the PPR is the earliest deteriorating parameter in acute and chronic graft dysfunction. In the MAG3 perfusion curve, the first phase that is up to the first pass peak and the second phase corresponding to early tubular extraction are present. Though the emergence of a flattened or descending curve pattern in the second phase, which has a rising tendency, is regarded as specific for graft dysfunction, it is not sensitive [16]. In our study, AR was detected in one patient and CrAN in two, whose second phase of the MAG3 perfusion curve was flattened. Values similar to those obtained with DTPA were obtained with MAG3 scintigraphy in 13 patients with normal graft function [17]. Tulchinsky et al. [18] found that MAG3 was an accurate indicator of prognosis in ARD. While studies in the literature regarding the importance of TP and TF values obtained with the Bubeck method are insufficient, it has been put forward by Bubeck that the TP points at ATN resolution and TF reflect the changes during rejection [3,5]. In our study, TP and TF values showed a negative correlation with HPI obtained with both agents and a positive correlation with PPR. Therefore we can conclude that lower values of TP and TF can indicate decreased allograft function. Kidney transplantation is the best treatment method in end-stage renal failure even in those carrying a high immunological risk and AR incidence decreases with immunosuppression [17]. The detection of AR with a renogram was reported to be more difficult in patients taking CyA [7,13]. In our study, all patients diagnosed with AR were taking CyA.

R20/3, which is a parameter showing close correlation with the severity of AR or ATN, was found to be high with both agents in patients diagnosed with AR in our study. It was stated that decreased cortical uptake of MAG3 can reflect irreversible damage [18]. Because the tubular extraction of MAG3 appears throughout the entire proximal tubules, it is affected by

ischemic damage or inflammation [19]. In our study, the most sensitive parameter for MAG3 in determining renal allograft dysfunction was R/B. A significant difference was detected between the Tmax values found with both agents in our study. The Tmax value which was normal with DTPA in eight patients was found to be prolonged with MAG3. In the images of these patients, a stasis was observed in the renal collecting system. When drawing the renal region of interest, care was taken to exclude collecting system activity. However, the counts were slightly affected due to a scattering effect.

There may be no increase in the serum creatinine concentration until 50% of kidney function is lost (in other words until the GFR falls by 50%). In our study, the GFR showed a negative correlation with the creatinine level. CrCl measurement may be very difficult and may not be very reliable in the evaluation of renal function. GFR measurements through a camera give more reliable information on renal functions [10,20,21]. In our study, a positive correlation was detected between GFR and CrCl.

Impairment in perfusion and parenchymal functions may occur for various reasons. Hence, their separation from one another is extremely important for early diagnosis and treatment. While I-131 OIH yields good results, the exposed radiation dose is relatively high. I-123 OIH may yield better results, but it is expensive and its free iodide concentration is quite high. Tc-99m MAG3 seems to be promising, although the quantitative data obtained must be translated into terms the transplantation team is familiar with. Doppler US mostly evaluates perfusion and the routine use of MRI is not realistic [22].

In conclusion, the peak/plateau pattern of the DTPA perfusion curve and the PPR parameter are more sensitive than HPI. We found DTPA to be more sensitive than MAG3 when perfusion and parenchymal function parameters were assessed together.

Competing interests

The authors declare that they have no competing interests.

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How to cite this article:
Ayaz S, Aktaş A, Moray G. DTPA and MAG3 scintigraphy in Acute Renal Allograft Dysfunction: Comparison of Diagnostic Values. J Clin Anal Med 2017;8(1): 14-8.